Pathophysiology of Renal Tubular Acidosis

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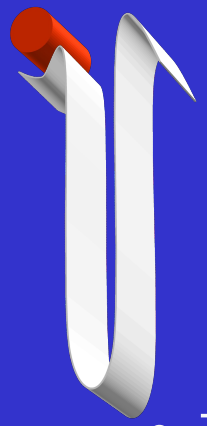
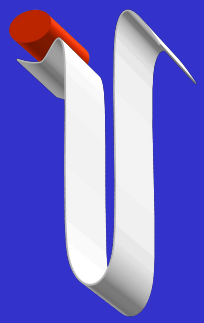


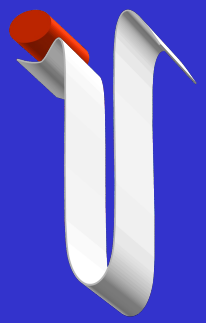
Objectives

- Define Renal Tubular Acidosis and its subtypes
- Understand the basic acid-base physiology of the proximal and distal nephron
- Apply tubular physiology to the understanding of Renal Tubular Acidosis
- Learn the pathophysiology and mechanisms underlying various subtypes of RTA



What is Renal Tubular Acidosis?

- Renal Tubular Acidosis (RTA) is a group of syndromes of renal tubular dysfunction characterized by either an impaired bicarbonate absorption or hydrogen ion secretion that is out of proportion to the glomerular filtration rate.

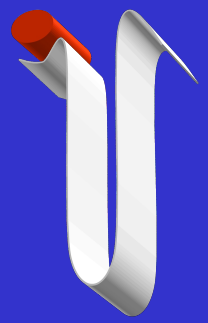


Renal Tubular Acidosis

- If this dysfunction is severe enough it will lead to a hyperchloremic metabolic acidosis (HCMA) with either hypokalemia, normokalemia or hyperkalemia depending on the defect leading to the RTA.

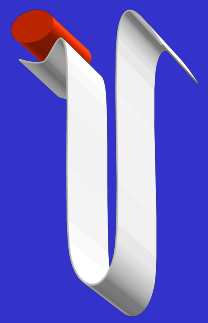
Renal Tubular Acidosis

- HCMA without renal insufficiency was first noted in the early 1930s
- Study of these syndromes lead to the term Renal Tubular Acidosis
- RTA is classically divided into 3 types.
  - Type I (distal RTA, dRTA)
  - Type II (proximal RTA, pRTA)
  - Type II RTA with Fanconi's Syndrome
  - Type IV RTA



General Principles

- Both volatile and nonvolatile acids are produced by normal daily metabolism.
- Approximately 15-20,000mmol/day of CO_2 are produced by the body and ventilated by the lungs.
- The average western diet produces 1.0-1.5 mEQ/kg/day of nonvolatile acids.

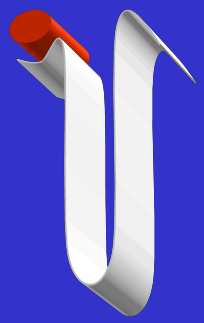


General Principles

These acids include:

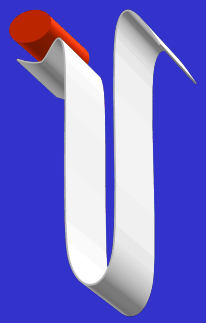
- Sulfurate from Methionine and Cystine
- Phosphoric acid from proteins and nucleic acids .

- Various organic acids from fat, protein, and nucleic acid metabolism.



General Principles

- Maintenance of acid-base balance requires the kidneys to conserve filtered bicarbonate (4300 mEQ/day) and excrete 50-100 mmol of noncarbonic acid.
- To do this three processes are crucial:
  1. Proximal reclamation of filtered HCO_3^-
  2. Synthesis and recycling of ammonium
  3. Distal secretion of hydrogen ions

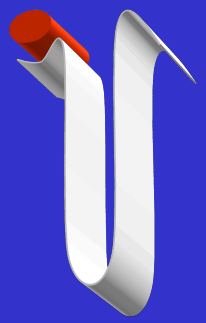


General Principles

- There is no significant urinary acid excretion of free hydrogen ions.
- Humans can lower urinary pH to about 4.5
- This correlates to a [H^+] of 0.03mEq/liter.
- For the average American diet of 70mEQ/day of nonvolatile acid >2,300 l/day would need to be produced to eliminate the daily acid load if buffers were not present

General Principles

- To rid itself of nonvolatile acids H^+ must be excreted bound to a base.
- This is done by binding H^+ to either ammonia or other nonbicarbonate buffers.
- The term used to define the amount of acid excreted is the Net Acid Excretion.
- NEA=(Titratable acid + NH_4^+) - urinary loss of bicarbonate.

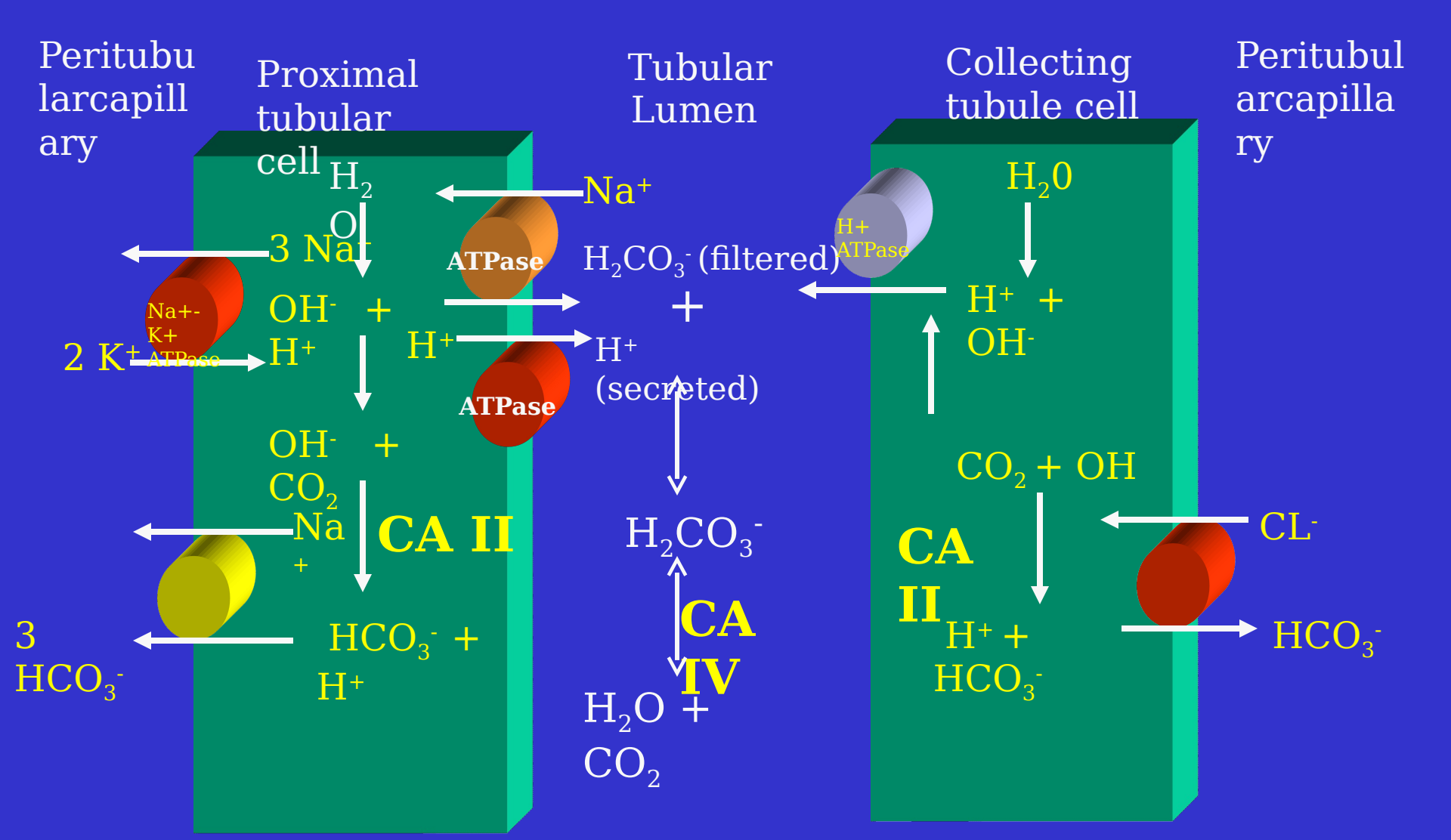


Proximal Tubule Physiology

- 80% of filtered bicarbonate is absorbed by the proximal tubule (PT).
- 10-15% by the thick ascending Loop of Henle (TAL) and the remainder by the distal Tubule (DT).
- Proximal bicarbonate reabsorption is mediated by two mechanisms:

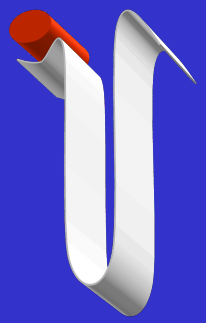
  Na^+-H^+-ATPase (66%)

  H^+-ATPase (33%)



CA - Carbonic Anhydrase

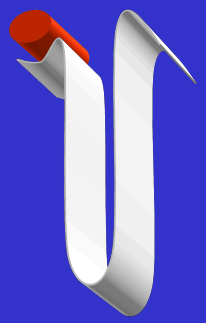
Adapted From Rose
Clinical Physiology of Acid
Base Disorders 4th Ed. Pg. 317



Proximal Tubule Physiology

- Ammonium synthesis and excretion is one of the most important ways kidneys eliminate nonvolatile acids.

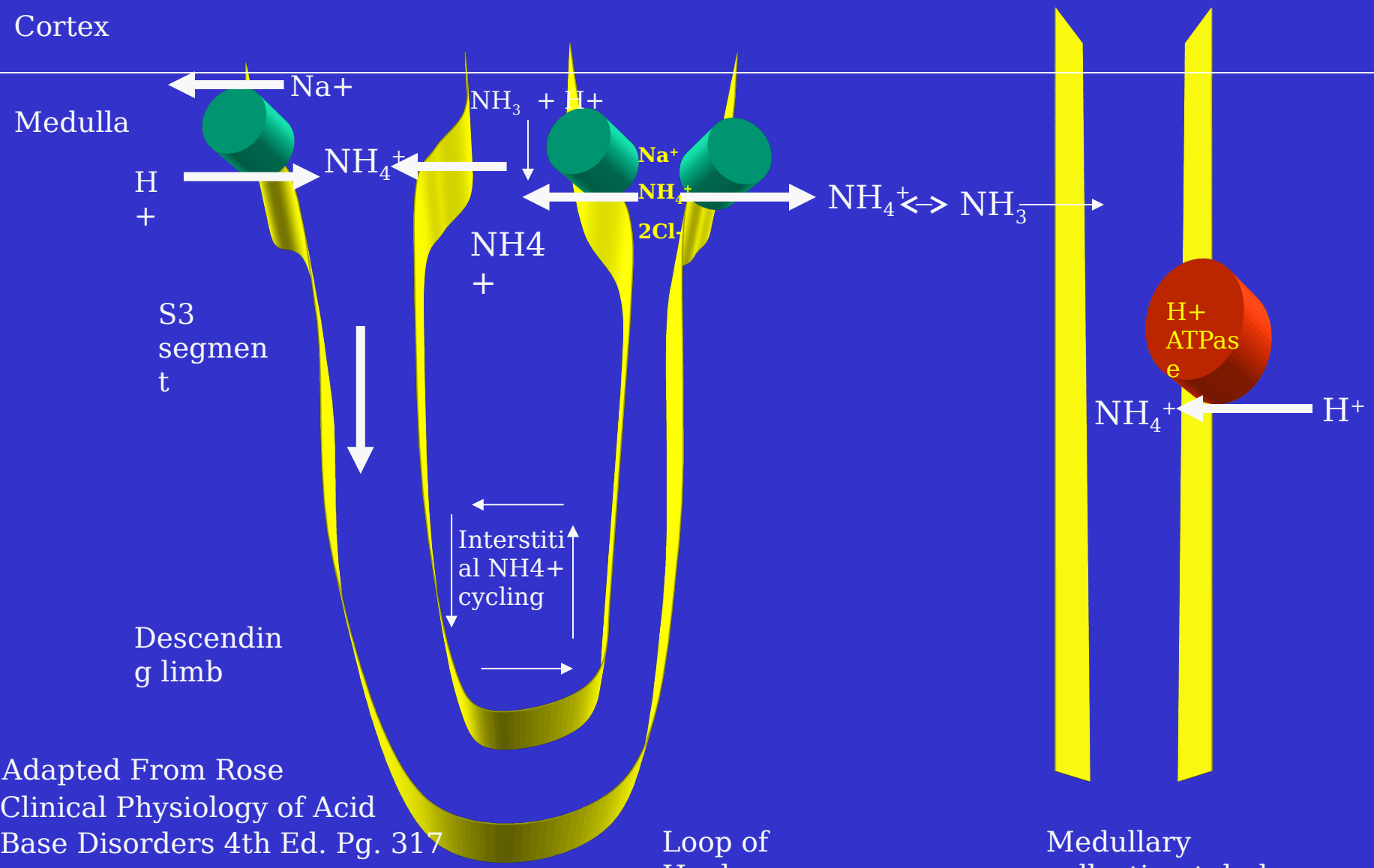
- Ammonium is produced via catabolism of glutamine.



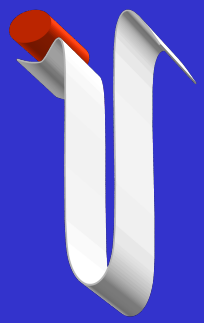
Proximal Tubule Physiology

- The net effect is 1 glutamine molecule is broken down into 2 NH_4^+ and 2 HCO_{3-},
- NH_4^+ is then secreted into the lumen by the Na^+/H^+ antiport by NH_4^+ substituting for hydrogen ions.
- 65-75% NH_4^+ is then actively absorbed by the TAL via substituting for K^+on the Na-K-2Cl pump. This is called medullary or interstitial recycling.

Ammonium Recycling



Adapted From Rose Clinical Physiology of Acid Base Disorders 4th Ed. Pg. 317

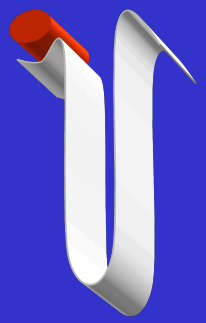


Proximal Tubule Physiology

- Total ammonium excretion is usually 30-40 mmol/24 hours but can be increased by up to 10 fold by increased glutamine metabolism in the Proximal Convoluted Tubule
- This accounts for > 90% of the kidney's ability to increase net acid excretion!

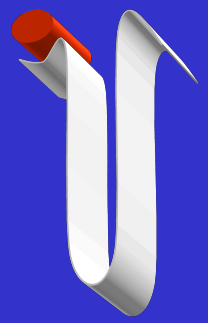
Collecting Tubule Physiology

- The collecting tubule (CT) is the major site of urinary acidification and is made up of the medullary collecting duct (MCT) and the cortical collecting duct (CCT).



Collecting Tubule Physiology

- Four cell types line the majority of the CT.
- Alpha and Beta-intercalated cells make up 40% of the lining while Principal cells and collecting tubule cells make up the remainder.



Collecting Tubule Physiology

- **Principal Cells** - primary sites of K^+ secretion and sodium/water reabsorption in the CT
- Sodium enters via and amiloride sensitive channel down a Na^+/K^+-ATPase induced gradient.
- Potassium exits via an apical conductance channel.

Collecting Tubule Physiology

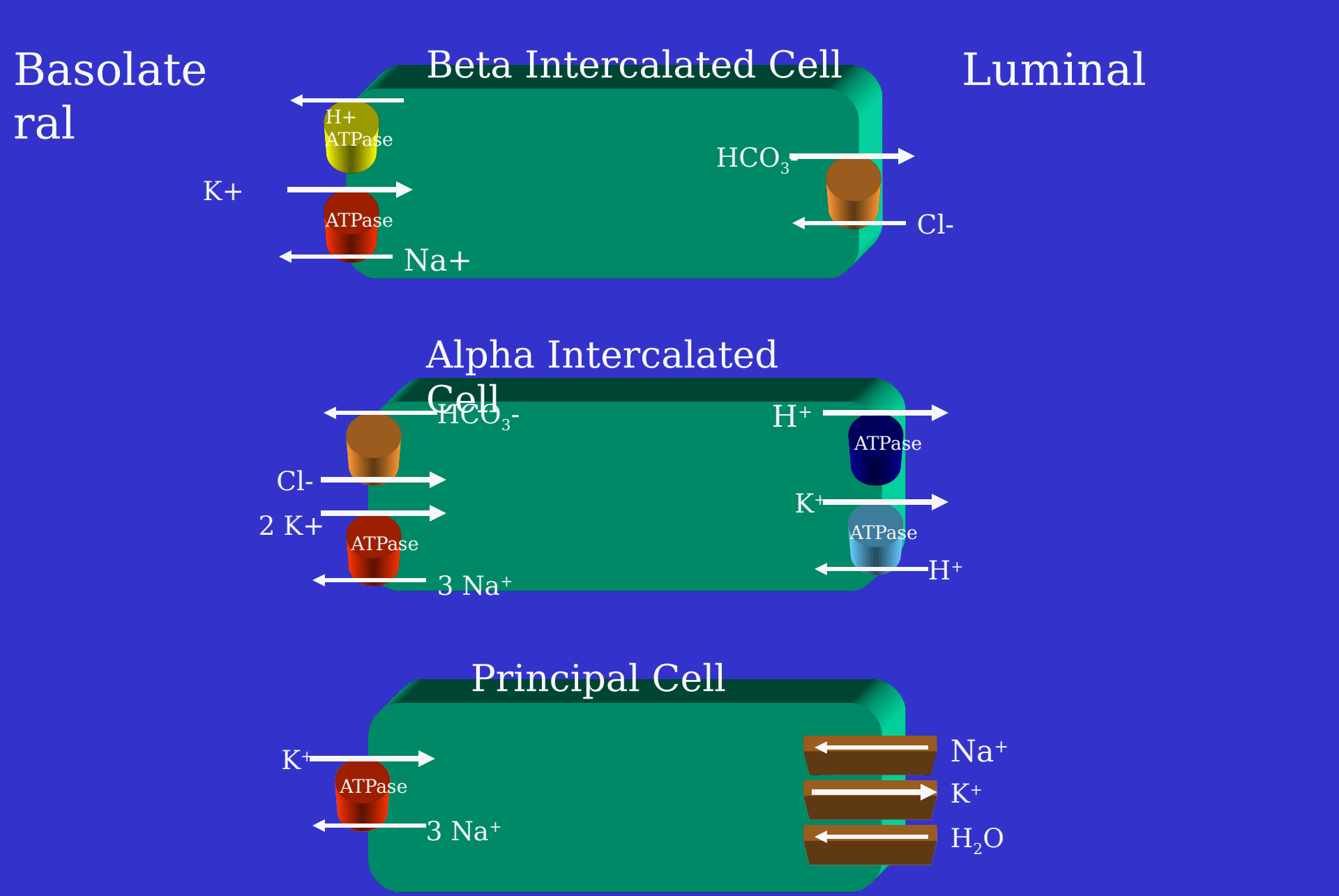
- During volume depletion the CT/principle cells can lower urinary sodium concentration to <5 mEQ/L.
- Aldosterone is the primary motivating factor for sodium reabsorption by increasing the Na^+- K^+ ATPase activity
- Aldosterone also increases sodium channels in the apical side of the cell (range from 100 to 3000).

Collecting Tubule Physiology

- Sodium entry is electrogenic and creates a lumen-negative gradient. This gradient helps promote both potassium and Hydrogen ion excretion.
- The Na^+- K^+ ATPase induced increase in intracellular K^+ is the primary determinant of urinary K^+ Secretion.

Collecting Tubule Physiology

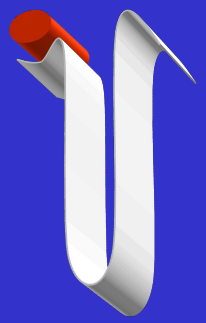
- **Alpha-Intercalated Cells** are thought to be the main cells involved with H^+ secretion in the CT. This is accomplished by an apically placed H^+-K^+-ATPase and H^+-ATPase with a basolateral Cl^-/HCO_3^- exchanger and the usual basolateral Na^+ - K^+ ATPase.
- **Beta-Intercalated Cells** in contrast to the above have a luminal **Cl^-/HCO_3^-** exchanger and a basolateral H^+-ATPase.



Adapted from: Battle, Flores: Underlying Defects in Distal Renal Tubular Acidosis AJKD Vol. 27, No 6, 1996 Pg. 899

Collecting Tubule Physiology

- CCT H^+ secretion is individually coupled to Na^+ transport. Active Na^+ reabsorption generates a negative lumen potential favoring secretion of H^+ and K^+ ions (Koeppen. Am J Physiol 242: 521-531, 1982)



Collecting Tubule Physiology

- In contrast the MCT secretes H^+ ions independently of Na^+. In this segment the lumen potential is positive presumably as a result of electrogenic H^+ secretion. (Stone: JCI 72:77-83, 1983 and Laski: JCI 72:2050-2059, 1983)

Collecting Tubule Physiology

- Both the CCT and MCT segments are sensitive to mineralocorticoid stimulation. In the MCT mineralocorticoids stimulate H^+ secretion that is sodium independent. In the CCT mineralocorticoids also stimulate H^+ secretion in part by sodium reabsorption. In addition H^+ secretion is directly stimulated by these hormones as evidenced by increasing lumen positive potential in the absence of luminal sodium.

Collecting Tubule Physiology

- In vivo data as to which segment is the most important in urinary acidification is lacking but in vitro studies in rabbits points to a higher acidification rate in the medullary portion of the tubule.

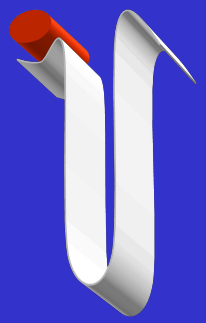
Collecting Tubule Physiology

- The cortical portion of the CT is unique in that it is capable of bicarbonate secretion and absorption depending on diet, acid-base balance and hormonal influences. This is because it is the only location for the beta-intercalated cells.

Collecting Tubule Physiology

Transporters

- Renal tubular epithelial cells are faced with the task of controlling hydrogen secretion by vacuolar ATPases as well as maintaining the activity of the various intracellular ATPases needed for cellular function.
- Hydrogen ion secretion is mediated by two types of proton pumps, a H^+-ATPase and a H^+-K^+-ATPase.



Collecting Tubule Physiology

- **H^+-ATPase** is a vacuolar ATPase (V-ATPase) responsible for a large proportion of the hydrogen ion secretion in the distal tubule. These V-ATPases are large multimeric proteins composed of 9 different polypeptides. They contain a catalytic domain termed V_1 that consists of A (70 kd) and B (56 kd) subunits arranged hexagonally around a D (33kd) subunit.

Collecting Tubule Physiology

- The A subunit contains the ATP hydrolysis site.
- The B subunit is thought to have a regulatory role and has two isoforms (B_1 and B_2). These isoforms are coded for by separate genes and expressed in

  different renal epithelial regions. The B_1 isoform is found only in intercalated cells while the B_2 isoform is found only in the proximal tubule.

Collecting Tubule Physiology

- Polarity in V-ATPase distribution allows the body the ability to either secrete bicarbonate during a metabolic acidosis or secrete hydrogen ions during a metabolic acidosis.
- This ability to change polarity and hence alter alpha and beta-intercalated cell density is termed plasticity
- Studies have shown only alpha-intercalated cells in the outer medullary tubule and hence no bicarbonate is excreted in this area.

Collecting Tubule Physiology

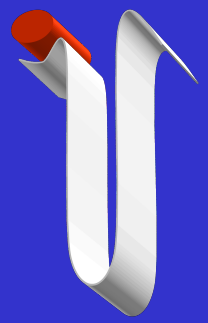
- **H^+-K^+-ATPase** Evidence of a K^+ stimulated ATPase was noted in 1987 by Doucet and Masry and 1988 by Garg and Narang. Their study indicated there was a potassium stimulated ATPase in the distal nephron that was independent of sodium

  reabsorption, insensitive to oubain and inhibited by omeprazole and SCH 28080.
- It was subsequently shown that this ATPase was stimulated by hypokalemia and inhibited by hyperkalemia.

Collecting Tubule Physiology

- Immunocytochemistry studies suggested the location of the transporter was the alpha-intercalated cells of the distal nephron.
- This H^+-K^+-ATPase is thought to be similar to the H^+-K^+-ATPase of the gastric mucosa but Western blot analysis by Bastani et al has failed to show expression of the of the protein.

  (Bastani J Am Soc Nephrol 3:772,1992)

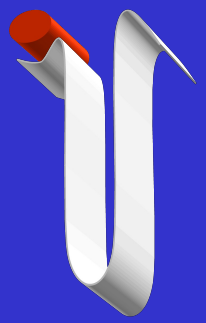


Types of RTA

- Traditionally RTA is subdivided into 3 forms.
- Proximal RTA (pRTA, Type II, Type II with Fanconi’s syndrome Type-II/FS)
- Distal RTA (dRTA, Type I)
- Type IV RTA
- These RTAs were named in the order in which they were discovered.

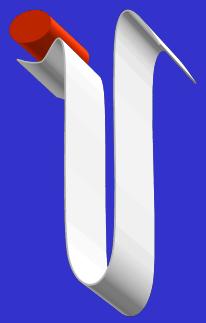
Types of RTA

- Type III RTA is a rare RTA seen in infants with evidence of both bicarbonate loss and impaired distal acid secretion. This is now thought to be just a variant of Type I with a transient bicarbonate wasting.



Proximal RTA

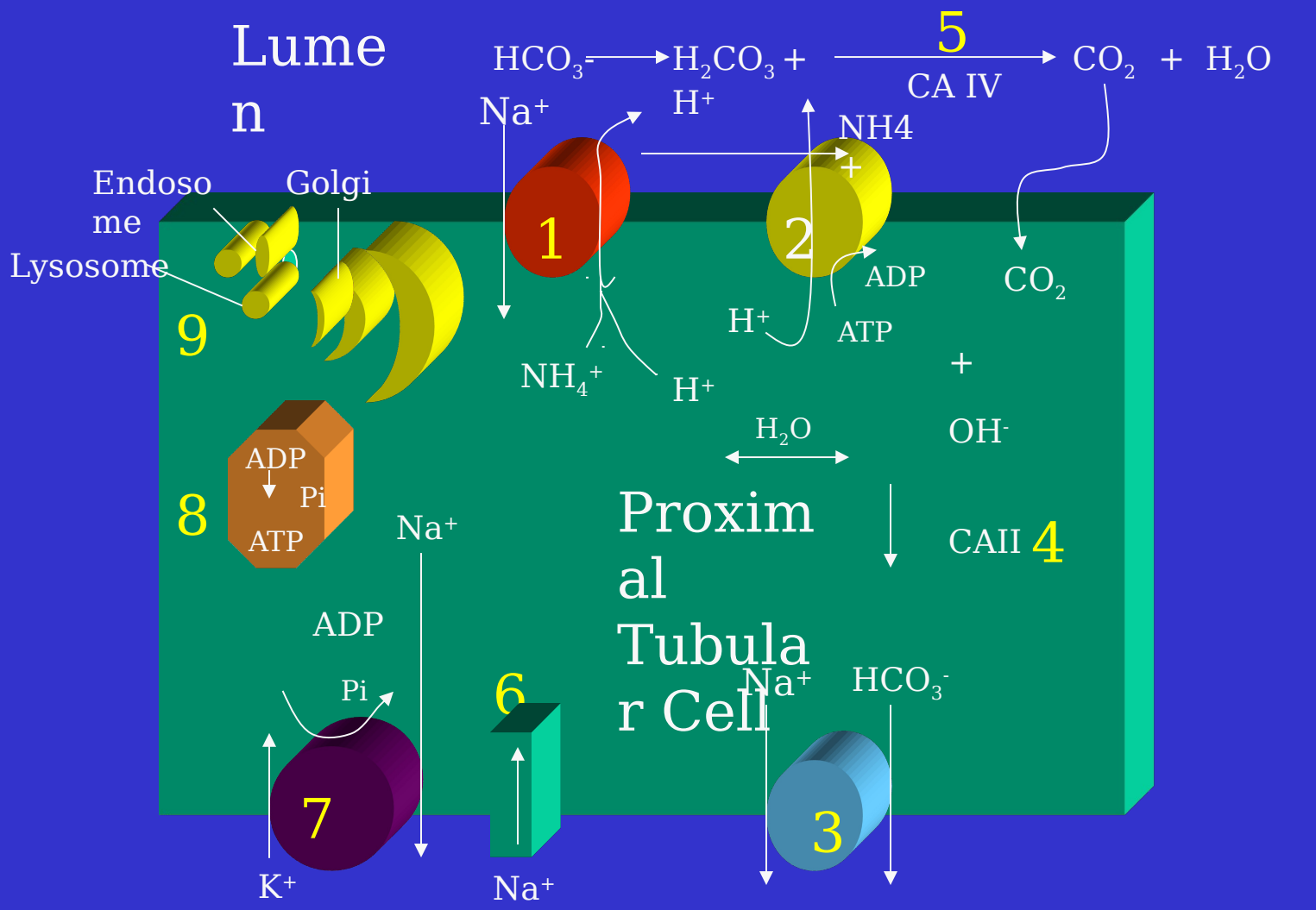
- Proximal RTA is a disorder leading to HCMA secondary to impaired proximal reabsorption of filtered bicarbonate.
- Since the proximal tubule is responsible for the reabsorption of 85-90% of filtered HCO_3^- a defect at this site leads to delivery of large amounts of bicarbonate to the distal tubule.



Proximal RTA

- The delivery of a bicarbonate rich filtrate to the distal tubule, which has limited reabsorption capabilities, leads to bicarbonaturia, kaliuresis and sodium losses.
- Thus patients will generally present with hypokalemia and a HCMA.

Potential Cellular Mechanisms Leading to Proximal RTA



Adapted from: Brenner and Rector's The Kidney 5th Ed. Pg. 1784

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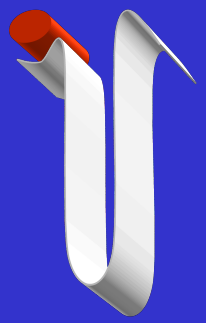
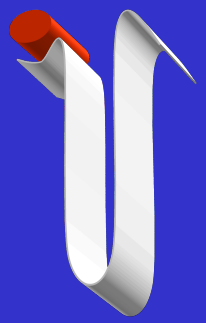


Proximal RTA

1. Na^+/H^+ antiport impairment which might also impair NH_4^+ secretion.
2. H^+-ATPase defects
3. Basolateral Na^+/HCO_3^- symportation
4. CA IV deficiency
5. CA II deficiency
6. Sodium Permeability defects
7. Na-K-ATPase deficiency
8. Inadequate Pi stores
9. Membrane recycling/ metabolism defects



Proximal RTA

- Proximal RTA is usually divided into two categories. An isolated bicarbonaturia and a generalized proximal tubular dysfunction manifested by the Fanconi syndrome.
- Defects in the first 5 mechanisms will lead to an isolated pRTA
- Defects in 5-9 leads to Fanconi’s Syndrome

Proximal RTA

- Fanconi Syndrome- A generalized proximal renal tubular dysfunction manifested by glycosuria, aminoaciduria, hypercitraturia, phosphaturia and bicarbonaturia leading to a HCMA.

Proximal RTA Differential Diagnosis

- Isolated pRTA (RTA-II)
- Primary (no obvious associated disease)
  - Sporadic
  - Hereditary
- Decreased CA activity
  - Heredity
  - Drugs (acetazolamide, sulfanilamide)
  - Osteopetrosis
- Cyanotic congential heart disease

Differential Diagnosis of pRTA Continued

- Generalized proximal tubular dysfunction (RTA-II/FS)
  - Primary
    - Hereditary
    - Sporadic
  - Genetic disease-Tyrosinemia, cystinosis, medullary
    - cystic dz, Wilson's dz, Lowe Syndrome, methylmalonic acidemia, pyruvate carboxylase deficiency, hereditary fructose intolerance

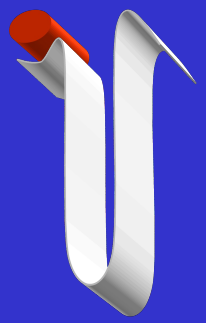
Differential Diagnosis of p RTA Continued

RTA-II/FS continued

- Acquired disorders
  - Dyspoteinemias (MG, MGUS, Amyloid, CLL)
  - Sjogren's Syndrome
  - Renal Vein Thrombosis
  - Chronic renal transplant rejection
- Drugs (outdated TCN, CSA, gentamicin, arginine, Pb, Mg
- Miscellaneous (paroxysmal hemoglobinuria, severe burns)

Proximal RTA

- **Hereditary Fructose Intolerance** is a due to a deficiency in Aldolase B that catalyzes the cleavage of fructose 1-phosphate. These patients develop a RTA-II/FS when ingesting fructose.
- This leads to an accumulation of fructose 1-phosphate and depletion of Pi with subsequent ATP depletion. The PCT is then without the ATP needed to drive cellular transport. Administration of Pi before exposure to fructose tends to blunt the development of pRTA in patients with HFI.



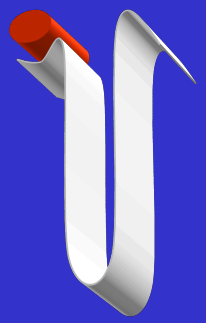
Proximal RTA

- **Cystinosis** is the most common cause of RTA-II/FS in children. The etiology is a defect in carrier-mediated transport of cystine that leads to massive accumulation of cystine in those children with homozygous cystinosis.
- This occurs throughout the kidney which is thought to impair mitochondrial oxidative phosphorylation

  (Coor, J Clin Invest 87:955-961, 1991)

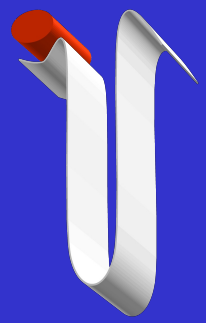
Proximal RTA

- There is also a cystinosis of adulthood with no renal disease and an adolescent or intermediate cystinosis which tends to have a moderate RTA-II/FS. Treatment with cysteamine has been shown to moderate the disease process in children.



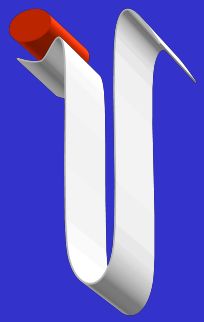
Proximal RTA

- **Vitamin D Deficiency** – a reversible RTA-II/FS has been described in patients with dietary vitamin D deficiency and those patients with genetically diminished vitamin D synthesis or resistance.
- Secondary hyperparathyroidism in and of itself is not enough to lead to suppression in renal acidification.
- Impairment of renal acidification has only been demonstrated in humans in conjunction with hypocalcemia, hypophosphatemia, and secondary HPT from vitamin D deficiency or a disordered vitamin D metabolism.



Proximal RTA

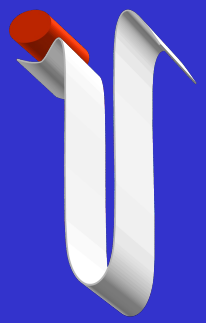
- **Wilson Disease -** The pRTA of Wilson Disease has not been studied extensively and appears in only a minority of patients. Patients with Wilson disease can have both a proximal and distal RTA.
- Pathogenesis of the pRTA is thought to be due to cellular deposition of copper in the proximal tubules and tends to get better with penicillamine administration.
- The dRTA however is thought to be from hypercalciuria and is not responsive to penicillamine.



Proximal RTA

- **Clinical Features**
- In pRTA the HCO_3^- threshold is lowered to approximately 12-20mmol/L. Once the serum HCO_3^- falls below this level the fractional excretion of bicarbonate falls off to normal

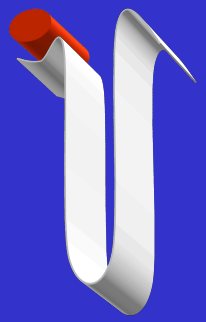
  levels and urinary pH usually drops below 5.5, as distal acidification is still intact. Because of this pRTA is usually a self-limited disorder
- Isolated defects in PCT function are rarely found. Most patients with a pRTA will have multiple defects in PCT function with subsequent Fanconi Syndrome.



Proximal RTA

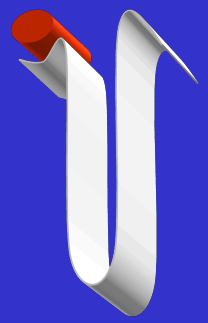
Patients with pRTA tend to be hypokalemic because:

1. Metabolic acidosis in and of itself decreases pRT Na^+ reabsorption leading to increased distal tubule delivery of Na^+ which promotes K^+ secretion.
2. The pRTA defect almost inevitably leads to salt wasting, volume depletion and secondary hyperaldosteronsim.
3. The rate of kaliuresis is proportional to distal bicarbonate Delivery. Because of this alkali therapy tends to exaggerate the hypokalemia.



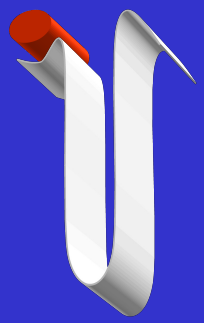
Proximal RTA

- Patients with pRTA usually have hypercalciuria but rarely develop nehrosclerosis or nephrolithiasis. This is thought to be secondary to high citrate excretion.
- In children, the hypocalcemia as well as the HCMA will lead to growth retardation, rickets, osteomalacia and an abnormal vitamin D metabolism. In adults osteopenia is generally seen.



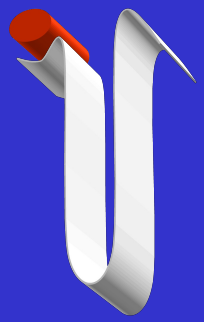
Distal RTA

- Distal RTA (RTA-I) is a disorder leading to HCMA secondary to diminished distal H+ secretion. Classically dRTA is a hypokalemic, HCMA with a urine pH >5.5 in the face of either a spontaneous or induced acidemia. It is often associated with hypercalciuria, hypocitraturia, nephrocalcinosis, and osteomalacia.
- Although described earlier it was first documented as a distinct entity by Albright, Parson and Burnett in 1946.
- The syndrome was termed dRTA because of the high urine pH found in these patients.



Distal RTA

- **Pathogenesis**
- As described earlier hydrogen ions are secreted by two different proton pumps located in the alpha intercalated cells of the collecting tubule, a H-ATPase and a H-K-ATPase.
- The H-ATPase is upregulated by aldosterone while the H-K-ATPase activity is inversely proportional to serum [K^+].
- Luminal H^+ then combine with either ammonia or other buffers and are excreted in the urine.



Distal RTA

Like pRTA multiple mechanisms are involved in the pathogenesis of dRTA. They include:

1. Secretory dRTA from a defective or absent proton pump "classical dRTA"
2. Permeability defect dRTA from back leak of protons into the cells of the distal tubule, also known as a gradient defect
3. Voltage-Dependent dRTA from an unfavorable electrical gradient for H^+ secretion.
4. NH_4^+ Synthesis/Transfer Defects dRTA secondary to insufficient supply of NH_3^+

Differential Diagnosis of dRTA

Secretory dRTA

Primary (no associated disease)

Sporadic

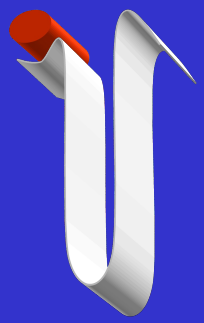
Hereditary

Genetic Disease

Ehlers-Danlos, Marfan's, sickle cell anemia,

eliptocytosis, medullary cystic disease, Fabry's,

Wilson's disease, congenital nerve deafness



Differential Diagnosis of dRTA

Secretory dRTA

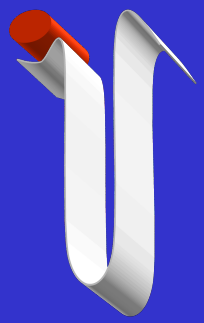
Autoimmune disorders

SLE, Sjogren's, Hypergammaglobulinemia, vasculitis, CAH, PBC, Cryoglobulinemia

Disease associated with nephrocalcinosis

Primary HPT, Vitamin D intoxication, Hyperthyroidism, Ideopathic hypercalciuria,

Hyperoxaluria, Fabry disease, Wilson disease



Differential Diagnosis of dRTA

Secretory dRTA

- Chronic pyelonephritis
- Chronic renal allograft rejection
- Hepatic cirrhosis
- Drugs (Toluene, NSAIDs, vanadate)

Differential Diagnosis of dRTA

Permeability defect (amphotericin B)

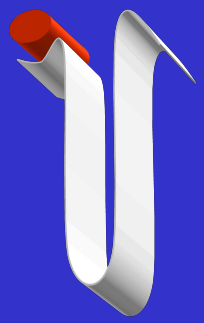
Voltage defect (Avid salt retention, amiloride)

Ammonium production defect

- Hyperkalemia
- Low GFR
- Interstitial disease

Combined defects

Postobstructive uropathy, Lithium, Interstitial Dz

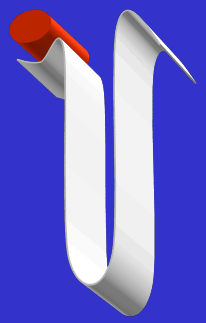


Distal RTA

Classic distal or Secretory dRTA- As discussed earlier secretory dRTA is a syndrome of hypokalemic, HCMA with a urine pH of >5.5 and an associated nephrocalcinosis,

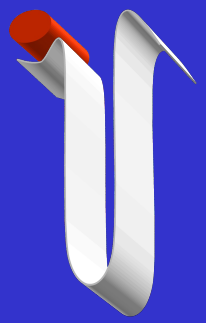
nephrolithiasis, and osteomalacia.

- In this version of dRTA the H-ATPase is thought to be either dysfunctional or absent leading to a decrease in H^+ secretion into the distal tubule lumen. The H-K-ATPase is also thought to be involved in some of the various dRTA subtypes.



Distal RTA

- A high urinary pH (5.5) is found in the majority of patients with a secretory dRTA.
- Excretion of ammonium is low as a result of less NH_4^+trapping. This leads to a positive urine anion gap.
- Urine PCO_2 does not increase normally after a bicarbonate load reflecting decreased distal hydrogen ion secretion.
- Serum potassium is reduced in 50% of patients. This is thought to be from increased kaliuresis to offset decreased H^+ and H-K-ATPase activity.



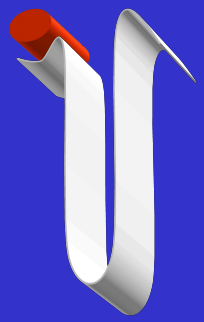
Distal RTA

Permeability Defect dRTA- this form of dRTA is caused by backleak of hydrogen ions from the lumen to blood in patients treated with amphotericin B.

- Urinary pH is usually >5.5
- Unlike classic dRTA urine PCO_2 does go up with acid loads.
- Alkali therapy usually decreases potassium losses since hydrogen ions will bind to the base and lead to more excretion.

Distal RTA
Permeability defect dRTA

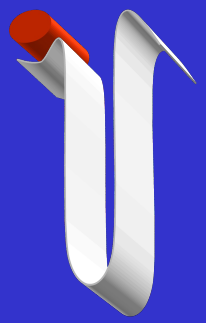
- Until recently this subtype of RTA has thought to always been from exposure to Amphotericin B.
- In 1996 Bonilla-Felix reported a case of an infant with a HCMA, low ammonium excretion, inappropriately high urine pH, but intact ability to increase urine $PCO_{2.}$. Lasix administration led to increased ammonium production and an increase in urine $PCO_{2..}$ The infant had not been exposed to Ampho B and was the first known primary PD-dRTA.
- (Bonilla-Felix: AJKD 27:428-430, 1982)



Distal RTA

Voltage-Dependent dRTA- An HCMA due to increased lumenal voltage. Sodium reabsoption in the renal tubules leads to a net electronegativity in the lumen. This negative gradient facilitates the distal tubule secretion of both H^+ and potassium.

- Thus when sodium resabsorption is decreased a voltage-dependent defect in H^+ and potassium secretion may ensue.
- This is often not a primary tubule disorder.



Distal RTA
Voltage-Dependent

Etiologies include:

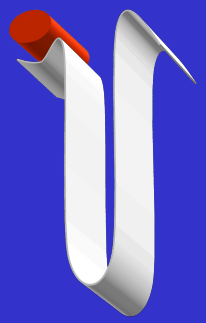
Severe intravascular volume depletion (Battle: NEJ:M 316:140, 1987)

Triamterene and amiloride

Sickle Cell disease (Batlle: Am J Med72:188, 1982)

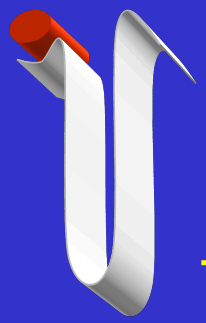
SLE (Bastani: JASN 4: 293, 1993)

Post obstruction



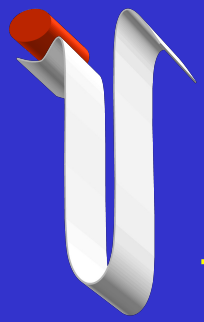
Distal RTA Voltage-Dependent

- Urinary pH is usually > 5.5
- Hyperkalemia can also be seen as potassium excretion is also voltage dependent
- Hyperkalemic dRTA may appear similar to a Type IV RTA.
- Aldosterone levels however are usually normal and the acidifying defect is more severe with a serum bicarbonate of < 15mmol/l in patients with V-D dRTA.
- In the Type IV RTA the serum bicarbonate is rarely <17mmol/l. (Batlle: NEJM 304:3731, 1981).



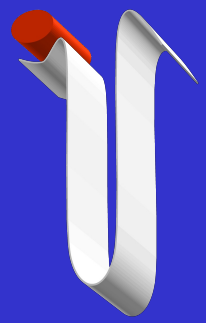
Distal RTA
Ammonium Synthesis-Transfer dRTA

- **NH4+ Synthesis-Transfer Defect dRTA**- As previously shown, the distal tubule is dependent on proton acceptors as well as an electronegative lumen environment to properly dispose of its acid load. Insufficient NH_3 states quickly exceed the phosphate buffer system leading to decreased lumen pH.
- This further inhibits hydrogen ion secretion.



Distal RTA
Ammonium Synthesis-Transfer dRTA

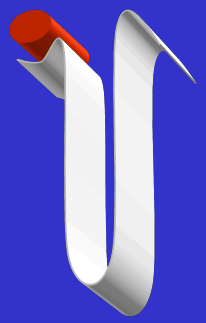
- Etiologies include:
- Decreased NH_3 synthesis seen with low GFRs.
- Decreased NH_3 reabsorption in the TAL.
- Impeded transfer in the interstitium.
- Severe prolonged hyperkalemia.
- Urinary pH is usually <5.5 in acidotic states as distal proton secretion is still intact.



Type IV RTA

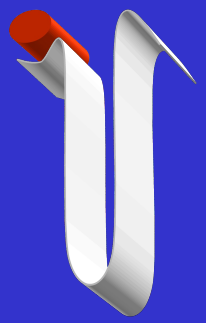
Type IV RTA is a typically hyperkalemic HCMA associated with a relative or absolute aldosterone deficiency.

- It is differentiated from dRTA by the patients ability to develop an acidic urine (<5.5) in acidotic states and from pRTA by its low FE_{HCO3^-}



Type IV RTA

- Pathogenesis:
- Thought to be secondary to decreased H-ATPase and Na-K-ATPase stimulation as well as decreased sodium conductance channel production.
- The sum total of the above is medullary recycling is dimished due to an intracellular alkalosis and hyperkalemia. This leads to diminished ammonium PCT synthesis and uptake in the TAL

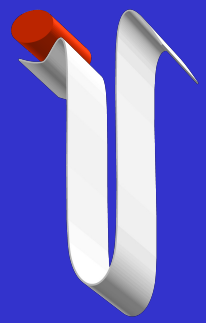


Type IV RTA

- Hyperkalemia can worsen the acidosis by inhibiting ammonium production.
- Patients generally present with a mild HCMA, hyperkalemia and ability to increase urine $PCO_{2.}$

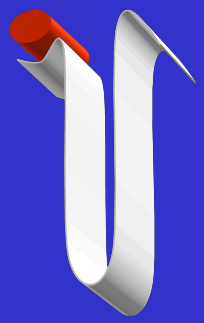
Differential Diagnosis Type IV RTA

- Aldosterone deficiency
  - Addison's disease
  - Bilateral adrenal destruction or removal
  - 21-Hydroxylase deficiency
  - 3B-ol-Dehydrogenase deficiency
  - Desmolase deficiency
  - AIDS



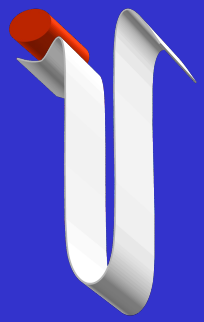
Differential Diagnosis Type IV RTA

- Isolated Aldosterone Deficiency
  - Familial hypoaldosteronism
  - Heparin
- Angiotensin-I inhibition
  - ACE-Is
  - Hyporeninemic Hypoaldosteronism
  - Nephrosclerosis
  - NSAIDs
  - HIV



Differential Diagnosis Type IV RTA

- Aldosterone Resistance
  - With salt wasting (psuedohypoaldosteronism)
    - Spironolactone
    - Tubulointerstitial nephritis
  - Without salt wasting
    - Hyporeninemia
    - Lupus Nephritis



Conclusion

- Renal Tubular Acidosis (RTA) is a group of syndromes of renal tubular dysfunction characterized by either an impaired bicarbonate absorption or hydrogen ion secretion that is out of proportion to the glomerular filtration rate.
- Understanding the basic physiology reviewed above will help one to recognize and characterize the various types of RTA as well as intuitively help decide what type of treatment is indicated in these patients.